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EXAMINER
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ART UNIT	PAPER NUMBER
1635	9

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/805,432	Applicant(s) BUSCHMANN ET AL.	
	Examiner J. Eric Angell	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6,8-13,15-20,22 and 23* is/are pending in the application.

4a) Of the above claim(s) *13,15-20,22 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 3 4 6 8-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This Action is in response to the communication filed on 10/23/02 as Paper No. 8. Claims 1, 3, 4, 6, 8-13, 15-20, 22 and 23 are pending in the application.

Election/Restrictions

2. Applicant's election with traverse of Group II (claims 1, 3, 4, 6, and 8-12), a method for enhancing arteriogenesis by administering a TGF-beta 1 protein, or a derivative or functionally equivalent substance in Paper No. 8 is acknowledged. The traversal is on the ground(s) that there is no serious burden to search additional groups because 1) the fields of search for all groups are highly overlapping, 2) most groups are classified in 514, 3) Groups I-VIII and XVII are all directed to methods for enhancing arteriogenesis, therefore it would not be a serious burden to search the therapeutic substances embodied in Groups I-VIII and the nucleic acid of XVII.

3. This is not found persuasive because although the groups may all be directed to methods of enhancing arteriogenesis, all of the groups are unrelated because the methods require the administration of patentably distinct compounds such as a nucleic acid, a protein, an antibody, and a small molecule. Furthermore, although the fields of search may overlap, the search required for each group is not completely coextensive with the searches required for the other groups because each group has unique search parameters. For instance, a search of polypeptides would not be coextensive with searches for, nucleic acids, antibodies, small molecules, etc. because the searches would require different search terms and in some instances different databases. Additionally, the Groups may have the same class designation, but they have

different sub-classifications (as set forth in the previous Office Action). Different sub-classification is prima facie evidence of a serious search burden.

Applicants point out that Inventions IX-XVI were indicated as being unrelated to each other because they are drawn to ex vivo administrations; however, claims 13 and 15-20 are not limited to ex vivo administration. In response it is acknowledged that claims 13 and 15-20 are not limited to ex vivo administration. However, Inventions IX-XVI are unrelated because each invention is drawn to the administration of a chemically distinct compound such as an antibody, nucleic acid, protein, small molecule, etc. Therefore, Inventions IX-XVI are unrelated as each is drawn to administration of patentably distinct substances, thus making Inventions IX-XVI unrelated inventions.

The requirement is still deemed proper and is therefore made FINAL.

4. Claims 13, 15-20, 22 and 23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 8. Claims 1, 3, 4, 6 and 8-12 are examined herein.

Specification

5. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (e.g. see page 16 of the specification). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

6. Additionally, the disclosure is objected to because of the following informalities: page 18 of the specification contains 3 lines of text and is otherwise blank.

Appropriate correction is required.

Drawings

7. New corrected drawings are required in this application because the figures of poor quality, especially Figures 6 and 7. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid **ABANDONMENT** of the application. **The requirement for corrected drawings will not be held in abeyance.**

Claim Objections

8. Claims 1 and 9 are objected to because of the following informalities: the claims encompass non-elected subject matter. For example, claim 1 encompasses both 1) TGF-beta 1 protein and 2) a nucleic acid encoding TGF-beta 1 and claim 9 encompasses an antibody, a polypeptide, a nucleic acid, a small organic compound, a ligand, a hormone, etc. However, the elected invention is a method of enhancing arteriogenesis by administering a TGF-beta 1 polypeptide or a derivative/functionally equivalent substance.

9. Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1, 3, 4, 6, and 8-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

12. While applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). The instant claims are drawn to a method for enhancing arteriogenesis wherein TGF-beta 1 (or a derivative or functionally equivalent substance; claims 8 and 9) is administered to a subject. In view of claim 9, wherein the derivative/functionally equivalent substance can be an antibody, nucleic acid, small organic compound, ligand, hormone, PNA or peptidomimetic, it appears that TGF-beat 1 can be an antibody, nucleic acid, small organic compound, ligand, hormone, PNA or peptidomimetic. However, the only acceptable meaning of "TGF-beta 1" recognized by one of skill in the art would be a TGF-beta 1 polypeptide. One of skill in the art would recognize, for example, an antibody specific for TGF-beta 1, but would not recognize the term "TGF-beta 1" as meaning an antibody.

Claim Rejections - 35 USC § 112, first paragraph

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 1, 3, 4, 6 and 8-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

It is respectfully pointed out that the claims are drawn to a method of enhancing arteriogenesis by administering TGF-beta 1 polypeptide or a derivative or functionally equivalent substance of TGF-beta 1 polypeptide (claim 1 in view of claim 8). Therefore, the claims encompass a genus of potentially millions of different molecules, considering every possible TGF-beta derivative (i.e., every possible substitution, deletion, addition, truncation, etc.). However, the specification only discloses one species of the claimed genus, TGF-beta 1 polypeptide. Therefore, the specification does not provide an adequate written description of the claimed genus of molecules encompassed by the claims.

The written description guidelines indicate that the description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species, by actual reduction to practice, by disclosure of relevant identifying characteristics (i.e. structure or other physical and/or other chemical properties), by disclosure of functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics sufficient to show applicant was in possession of the claimed genus." (See MPEP 2164).

Regarding the description of a representative number of species, the guidelines note "a satisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the applicant was in possession of the **necessary common attributes or**

features of the elements possessed by the members of the genus in view of the species disclosed." (Emphasis added; see: Federal Register: December 21, 1999, Volume 64, Number 244; revised guidelines for written description). In the instant case, only one species of the genus is describes (the TGF-beta 1 polypeptide). There is no disclosure describing any derivatives or substances which are functionally equivalent to TGF-beta 1. No common attributes or features possessed by the genus of molecules encompassed by the claims are disclosed. There is no indication of any relevant structural/chemical characteristics common to the genus of molecules, and no identification of any structural limitations/requirements which provide guidance on the identification of molecules that meet the functional limitations.

In the application at the time of filing, there is no record or description which would demonstrate conception of any TGF-beta 1 derivative or functionally equivalent substance which have the claimed function. Therefore, the claims fail to meet the written description requirement by encompassing molecules which are not described in the specification.

15. In view of the written description rejection above and for the reasons set forth below, claims 1, 3, 4, 6 and 8-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for enhancing arteriogenesis and/or the growth of collateral arteries and/or other growth of other arteries from said collateral arteries in mammals, wherein the method comprises delivery of TGF-beta 1 polypeptide directly into the collateral arteries of said mammals, does not reasonably provide enablement for the method wherein a TGF-beta 1 derivative or functionally equivalent molecule is administered, or wherein the TGF-beta 1 is not locally delivered into the collateral circulation. The specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claims are drawn to a method for enhancing arteriogenesis and/or growth of collateral arteries and/or other arteries from preexisting arteriolar connections by administering TGF-beta1 polypeptide or a derivative or functionally equivalent molecule. Therefore, the nature of the invention is modulation of arteriogenesis/artery growth for therapeutic purposes by administration of a pharmaceutically active compound.

The breadth of the claims

The breadth of the claims is very broad. For instance the claims encompass administering any TGF-beta 1 polypeptide derivative or functionally equivalent substance, for treating any vascular disease or cardiac infarct in any species of animal, including humans.

The unpredictability of the art and the state of the prior art

There are a number of problems recognized in the art with respect to administration of a protein pharmaceutical for treatment of disease, and specifically with the treatment to enhance arteriogenesis.

For instance, Shire in Biopharmaceutical Drug Design and Development (Wu-pong et al. Eds, Humana Press; Chapter 9; pages 205-238) teaches some of the problems associated with protein as pharmaceutical agents. Specifically, Shire teaches,

> "The formulation of protein therapeutics is more difficult than for traditional small-molecule drugs, because of the complex composition and physical properties of the proteins. In particular, the importance of maintaining protein confirmation makes this task especially difficult. Loss of protein activity or increased immunogenicity can result without any covalent chemical modifications. Many of the degradative pathways in proteins, such as proteolysis, deamidation, oxidation, or self-association, will be subject to a diverse set of solution conditions. Generally, especially for a liquid formulation, it is not possible to produce a formulation that will eliminate all of the potential routes of inactivation." See paragraph bridging pages 231-232.

Scholz et al. (Angiogenesis Vol. 4; p. 247-257; 2001) indicates the unpredictable nature of arteriogenesis as a therapeutic method for treating vascular diseases. Specifically, Scholz teaches,

> "Collateral vessels exhibit the same morphology whether they had formed in the heart, limbs or brain or in dogs, rabbits or mouse. They are tortuous because they also increase lengthwise in a restricted space. In animals larger than the mouse, they develop an intima, and initially, many arterioles participate in arteriogenesis, but only a few mature into large arterial channels which, when arterial occlusion had preceeded slowly enough, can replace the occluded artery to a significant proportion. Therapy with a single growth factor in animals with occluded femoral arteries significantly increased the speed of arteriogenesis but does not significantly increase the level of adaptation. It appears that the mastergene for arteriogenesis still awaits discovery." (See p. 247, abstract).

Therefore, it is unpredictable that a protein therapy could be effectively used to treat any vascular disease.

Working Examples and Guidance in the Specification

The specification indicates one example where TGF-beta polypeptide (0.48 ug/kg/day) was locally administered directly into the collateral circulation of rabbits comprising a femoral artery ligation (see example 3, p. 20-23). It is disclosed that "TGF-beta 1 infusion for a time period of one week had significantly increased the number of visible collateral arteries as compared to the PBS-control group... The results of the experiments performed in accordance with the present invention indicate that TGF-beta 1 is capable of mediating arteriogenesis, and/or the growth of collateral arteries and/or other arteries from preexisting arteriole connections by activation of the monocyte/macrophage pathway" (see p. 22, second and third paragraphs).

There is no indication that administration of the TGF-beta 1 polypeptide by any means other than direct delivery into the collateral arteries can stimulate arteriogenesis and/or growth of collateral arteries and/or growth of other arteries from said collateral arteries. Furthermore, there is no indication that the treatment could effectively treat any vascular disease such as cardiac infarct or stroke.

Quantity of Experimentation

Additional experimentation is required in order to overcome unpredictable nature of protein therapy in general and the unpredictable nature of therapeutic arteriogenesis recognized in the art and effectively use the claimed method to the full scope encompassed by the claims. For instance, experimentation would have to be done in order to effectively deliver a protein therapeutic agent by any means other than direct delivery in order to avoid protein degradation pathways (and the hosts immune response). Furthermore, one would have to show that the

administration could effectively stimulate enough arteriogenesis or collateral (or other) artery growth effective to treat any vascular disorder including cardiac infarct, stroke, etc.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the high degree of unpredictability recognized in the art, the breadth of the claims, the limited of working examples and guidance in the specification; and the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed method is undue.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell
December 24, 2002

DAVE T. NGUYEN
PRIMARY EXAMINER